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APPLICATION NO	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO	CONFIRMATION NO
09/600,493	07/18/2000	Jack Wands	MGH-0026	3498

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EXAMINER
SHUKLA, RAM R

ART UNIT	PAPER NUMBER
2632	11

DATE MAILED: 09/24/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/600,493	Applicant(s) WANDS ET AL.
	Examiner Ram Shukla	Art Unit 1632

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 June 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *3,4,7,8,11-28 and 32-46* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *3,4,7,8,11-28 and 32-46* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *detailed action* .

DETAILED ACTION

1. Applicants' amendment and response to the Office Action filed 6-26-02 have been received.

2. Claims 6, 13, 32 and 45 have been amended.

3. Claims 3, 4, 6-8, 11-28 and 32-46 are under consideration.

4. The utility rejection of claims 3, 4, 6-8, 11-28, and 32-46 has been withdrawn in the view of the applicants' arguments.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 3, 4, 6-8 11-28 and 32-46 rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention, for reasons of record set forth in the previous office actions of 8-2-01 and 3-28-02.

It is noted that applicants' amendment has removed the limitation of "optionally" from the independent claims 6, 13, 32 and 45. Accordingly, claimed invention will comprise the 5' UTR of hepatitis C virus. Since in the previous office action, a scope rejection was set forth in view of the invention reading on a composition lacking 5' UTR and now as amended claims do not encompass such as nucleic acid composition, a full lack of enablement is set forth as was applicable to claims 11-28 and 32-46 and discussed in the previous office actions of 8-2-01 and 3-28-02. A new art used in the enablement rejection (discussed below; Selby et al) was used as a result of amendment.

Response to Arguments

Applicant's arguments filed 6-26-02 have been fully considered but they are not persuasive. Applicants have argued that office action does not provide any

support for its position. Further, applicants argue that the office action does not identify what undue experimentation would be required and that it is irrelevant to enablement whether the function of 5' UTR is known or not. Next, applicants cite an article by Tokushige et al (PNAS 1996) in support of their argument that an artisan knows how to make a construct with 5' UTR region. First, applicants have ignored the arts and the sound scientific reasoning set forth on pages 5 and 6 of the office action of 3-28-02 and pages 3-7 of the office action of 8-2-01. Next, the issue of function of 5' UTR is not irrelevant because that would be the basis of why an artisan would add 5' UTR to a nucleic acid construct. Next, the art of Tokushige et al does not teach a construct comprising NS4 or NS5 and 5' UTR, rather Tokushige et al used a long fragment of HCV that comprised a core protein and 5' UTR. It is noted that 5' UTR and core encoding sequences are present next to each other in the viral genome. Therefore, the construct of Tokushige in now way provides how to make a construct that comprises a promoter, enhancer NS4 or NS5 encoding sequences and 5' UTR. It is noted that the 5' UTR and the sequences encoding the nonstructural proteins of HCV are present at two different ends and there is no operational linkage between the two sequences in terms of any regulatory functions of 5' UTR. Additionally, it is noted that full length 5'UTR inhibits expression of viral genes (see first full paragraph on page 1105 right column in Selby et al J. Gen. Virol. 74:1103-1113, 1993). Selby et al further observed that 5' leader does not promote efficient translation. This clearly indicates that expression from a construct comprising 5' UTR would produce lower levels of gene expression and it is not clear whether the claimed construct would produce sufficient protein to produce an immune response. It is reiterated that applicants in their working examples used a construct that did not have the 5' UTR. Therefore, expression level with the construct in the working example cannot be compared with the expression level with the construct instantly recited.

Next applicants have argued that claims do not recite methods of inducing a "protective" immune response and that the office has improperly imported limitation from the specification. However, applicant's arguments are irrelevant since the claims are drawn to a pharmaceutical composition and a pharmaceutical

composition is for treatment and in the instant case it would be protective immunity. Applicants' reference to In Erlich is misplaced since the issue in Erlich was not treatment. Applicants' arguments that any amount of immune response would be considered a therapeutic amount are not persuasive. Applicants have not provided any evidence to support their statement. It is noted that applicants' argument alone cannot take place of evidence lacking in the record (see In re Scarbrough 182 USPQ, (CCPA) 1979).

Next, applicants argue that Houghton et al does not support the position taken in the office action rather it supports that the specification is enabling and mouse is a model. However, applicants seem to have completely ignored the discussion of Houghton on page 334, last paragraph that discusses the challenges of immunization for HCV. For example, they noted that the delivery of the HCV nucleic acid needs to be optimized since most mouse protocols involve injection of several hundred micrograms of DNA in order to get generally weak immune response. It is noted that the specification does not provide any guidance as to how the method would be adopted or optimized for another animal. Additionally, Houghton et la notes that nonstructural proteins, such as NS3 are transforming when tested in NIH3T3 cells and are tumorogenic in nude mice. While it is agreed that PTO is not responsible for safety issues, transforming activity and tumorigenic potential would have effect on immunization. In other words, an artisan has to examination the evidence and discussion of Houghton et al in its totality.

Next, Applicants have argued that Encke et al teaches that a mouse is an animal model for inducing immune response. The issue is: can mice be animal models for immunization against HCV. Applicants' are directed to the last but one sentence of Encke et al on page 4922, which states that DNA based immunization with genes encoding non-structural proteins, is an attractive approach... However the clinical efficacy of the approach needs to be evaluated. When one considers the teachings and discussions of Houghton et al and Encke et al in totality, results obtained in a mouse model cannot be predictive of results in other primates or humans. Finally, discussing Chattergoon et al, applicants argue that they are not claiming complete protective immunity rather a method for inducing immune

response. However, applicants ignore the intended use of inducing immunity, i.e. for treatment as has been emphasized again and again in the office action. The specification as filed does not provide sufficient guidance as to how an artisan of skill would have extrapolated the methods used in mouse to other animals and induce immune response in view of the discussion above of the state of the art of DNA based immunization, mouse as an animal model for HCV and role of 5' UTR in regulation of gene expression. Therefore, in view of the breadth of the claims and the lack of guidance provided by the specification as well as the unpredictablility of the art, one of ordinary skill in the art at the time of the invention would have required an undue amount of experimentation to make and use the invention as claimed.

7. The 102 rejection has been withdrawn in view of the amendment to claims.

8. It is noted that Selby et al J. Gen.Virol. 74:1103-1113, 1993 (ref BM in the IDS filed 207-01 has not been applied since it does not teach a construct comprising an enhancer. Selby et al teaches several constructs for expression of viral proteins. For example, the plasmid pHCV comprises the entire viral genome (see the methods section on page 1103, right column continued into the left column on page 1104 and figure 1). The plasmids pHCV5-1 and pHCV comprise the entire 5'UTR and 3'UTR and the coding sequence for the non-structural proteins. Since the protein of the virus is produced as a polyprotein, a fusion of NS4-NS5 would be produced as a result of partial proteolytic digestion.

9. No claim is allowed.

10. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is

filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

When amending claims, applicants are advised to submit a clean version of each amended claim (without underlining and bracketing) according to § 1.121(c). For instructions, Applicants are referred to http://www.uspto.gov/web/offices/dcom/olia/aipa/index.htm. Applicants are also requested to submit a copy of all the pending/under consideration claims.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ram R. Shukla whose telephone number is (703) 305-1677. The examiner can normally be reached on Monday through Friday from 7:30 am to 4:00 p.m. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Reynolds, can be reached on (703) 305-4051. The fax phone number for this Group is (703) 308-4242. Any inquiry of a general nature, formal matters or relating to the status of this application or proceeding should be directed to the Dianiece Jacobs whose telephone number is (703) 305-3388.

Ram R. Shukla, Ph.D.

RAM R. SHUKLA, PH.D
PATENT EXAMINER